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*Published in:*  
Kidney International Reports

*DOI:*  
[10.1016/j.ekir.2018.03.005](https://doi.org/10.1016/j.ekir.2018.03.005)

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*Document Version*  
Publisher's PDF, also known as Version of record

*Publication date:*  
2018

[Link to publication in University of Groningen/UMCG research database](#)

### *Citation for published version (APA):*

Esmeijer, K., Geleijnse, J. M., de Fijter, J. W., Giltay, E. J., Kromhout, D., & Hoogeveen, E. K. (2018). Cardiovascular Risk Factors Accelerate Kidney Function Decline in Post-Myocardial Infarction Patients: The Alpha Omega Cohort Study. *Kidney International Reports*, 3(4), 879-888.  
<https://doi.org/10.1016/j.ekir.2018.03.005>

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# Cardiovascular Risk Factors Accelerate Kidney Function Decline in Post–Myocardial Infarction Patients: The Alpha Omega Cohort Study



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**Introduction:** Impaired kidney function is a robust risk factor for cardiovascular mortality. Age-related annual kidney function decline of 1.0 ml/min per 1.73 m<sup>2</sup> after age 40 years is doubled in post–myocardial infarction (MI) patients.

**Methods:** We investigated the impact of the number of cardiovascular risk factors (including unhealthy lifestyle) on annual kidney function decline, in 2426 post-MI patients (60–80 years) of the prospective Alpha Omega Cohort study. Glomerular filtration rate was estimated by serum cystatin C (eGFR<sub>cysC</sub>) and combined creatinine–cystatin C (eGFR<sub>cr-cysC</sub>), using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations from 2012. Data were analyzed by multivariable linear and logistic regression.

**Results:** At baseline, mean (SD) eGFR<sub>cysC</sub> and eGFR<sub>cr-cysC</sub> were 81.5 (19.6) and 78.5 (18.7) ml/min per 1.73 m<sup>2</sup>, respectively. Of all patients, 79% were men, 19% had diabetes, 56% had high blood pressure ( $\geq 140/90$  mm Hg), 16% were current smokers, 56% had high serum low-density lipoprotein (LDL of  $\geq 2.5$  mmol/l), and 23% were obese (body mass index of  $\geq 30.0$  kg/m<sup>2</sup>). After multivariable adjustment, the additional annual eGFR<sub>cysC</sub> decline (95% confidence interval) was as follows: in patients with versus without diabetes,  $-0.90$  ( $-1.23$  to  $-0.57$ ) ml/min per 1.73 m<sup>2</sup>; in patients with high versus normal blood pressure,  $-0.50$  ( $-0.76$  to  $-0.24$ ) ml/min per 1.73 m<sup>2</sup>; in obese versus nonobese patients,  $-0.31$  ( $-0.61$  to  $0.01$ ) ml/min per 1.73 m<sup>2</sup>; and in current smokers versus nonsmokers,  $-0.19$  ( $-0.54$  to  $0.16$ ) ml/min per 1.73 m<sup>2</sup>. High LDL was not associated with accelerated eGFR<sub>cysC</sub> decline. Similar results were obtained with eGFR<sub>cr-cysC</sub>.

**Conclusion:** In older, stable post-MI patients without cardiovascular risk factors, the annual kidney function decline was  $-0.90$  ( $-1.16$  to  $-0.65$ ) ml/min per 1.73 m<sup>2</sup>. In contrast, in post-MI patients with  $\geq 3$  cardiovascular risk factors, the annual kidney function decline was 2.5-fold faster, at  $-2.37$  ( $-2.85$  to  $-1.89$ ) ml/min per 1.73 m<sup>2</sup>.

*Kidney Int Rep* (2018) 3, 879–888; <https://doi.org/10.1016/j.ekir.2018.03.005>

KEYWORDS: cardiovascular risk factors; kidney function decline; lifestyle

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The incidence of chronic kidney disease (CKD) shows an increasing trend worldwide.<sup>1</sup> Impaired kidney function is a robust and independent risk factor for cardiovascular and all-cause morbidity and mortality.<sup>2</sup> In industrialized countries, in healthy individuals after age 40 years, kidney function gradually declines annually about 0.8 to 1.0 ml/min per 1.73 m<sup>2</sup>.<sup>3,4</sup> In contrast, post–myocardial infarction (MI) patients have an accelerated kidney function decline of about

2.2 ml/min per 1.73 m<sup>2</sup> per year, and are thus more prone to developing CKD.<sup>5</sup>

Classic modifiable cardiovascular risk factors such as hypertension and diabetes are important drivers for the development of CKD.<sup>6–10</sup> The association between elevated low-density lipoprotein (LDL) levels and kidney function decline is less clear.<sup>11</sup> Lifestyle factors, such as cigarette smoking and adiposity, may increase the risk of hypertension and diabetes. All previously mentioned cardiovascular risk factors can have an unfavorable effect on kidney function owing to increased inflammation, oxidative stress, endothelial dysfunction, and disturbed coagulation. For example, accumulation of visceral adipose tissue may lead to increased

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Received 7 December 2017; revised 16 February 2018; accepted 12 March 2018; published online 16 March 2018

production of inflammatory mediators by adipocytes, which may contribute to glomerular and interstitial fibrosis.<sup>12,13</sup>

Survival after MI has been improving, as a result of improved health care and pharmaceutical treatment. These trends, together with the global tendency toward a less healthy lifestyle and population aging, have resulted in a considerable pool of patients at high risk for CKD.<sup>14</sup> Little is known about the beneficial effect of optimal treatment of cardiovascular risk factors and healthy lifestyle on kidney function decline in post-MI patients. Because adequate drug treatment of cardiovascular risk factors and modest lifestyle alterations are achievable and may retard kidney function decline in post-MI patients, we studied the association of modifiable cardiovascular risk factors (including lifestyle) in older, stable post-MI patients in the Alpha Omega Cohort.

## METHODS

### Study Participants

This is a secondary analysis of the prospective Alpha Omega Cohort Study ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT03192410) no. NCT03192410). We included patients from the Alpha Omega Trial, a randomized, controlled, multicenter trial of omega-3 (n-3) fatty acids supplementation in 4837 patients with a verified history of MI. Patients were 60 to 80 years of age and were receiving state-of-the-art antihypertensive, antithrombotic, and lipid-modifying drug treatment, according to international guidelines, as described elsewhere.<sup>15,16</sup> The trial started in 2002 and ended in 2009. Patients with severe heart failure (New York Heart Association [NYHA] stage IV) were excluded. For the present observational study, patients were selected from whom nonfasting blood was drawn at baseline and after 41 months. Owing to financial constraints, 2 blood samples were available only for 2426 patients (50% of the cohort, i.e., those randomized before August 2005). Of all patients randomized before August 2005 [ $n = 2918$ ], 233 patients died during follow-up, and 259 patients had missing blood samples or refused participation ([Supplementary Figure S1](#)). This study was conducted in accordance with the Declaration of Helsinki and was approved by a central medical ethics committee in the Netherlands. Written informed consent was obtained from all patients. Design and reporting of the current study was performed in accordance with the Strengthening The Reporting of OBservational Studies in Epidemiology (STROBE) Statement for cohort studies.<sup>17</sup>

### Data Collection

Patients were interviewed and physically examined by trained research nurses at baseline and after 41 months.

Standardized blood handling procedures for the Alpha Omega Trial are described in detail elsewhere.<sup>18,19</sup> Lipid, glucose, and high-sensitivity C-reactive protein (hsCRP) levels were determined as described elsewhere.<sup>20</sup> Information on demographic variables, lifestyle habits, current health status, and medical history were collected by self-administered questionnaires as previously described in detail.<sup>18</sup> Questionnaires were checked by research nurses. Information on smoking of cigarettes was obtained by self-reported questionnaires and was dichotomized into current smoking versus nonsmoking (former or never smoking). Alcohol consumption was dichotomized into  $\geq 1$  glass per week versus  $< 1$  glass per week. Systolic and diastolic blood pressure (first and fifth Korotkoff sounds, respectively) were measured at the left upper arm with the patient seated, after a 10-minute seated rest, using an automatic device (Omron HEM-711, Omron Healthcare Europe B.V., Hoofddorp, The Netherlands). The average of 2 blood pressure measurements was taken. High blood pressure was defined as inadequately controlled blood pressure according to the latest recommendations of the international guideline of the European Society of Cardiology (systolic blood pressure  $\geq 140$  mm Hg or diastolic blood pressure  $\geq 90$  mm Hg).<sup>21</sup> Diabetes mellitus was considered to be present in case of a self-reported physician diagnosis, use of glucose-lowering drugs, and/or hyperglycemia. Hyperglycemia was defined as serum glucose of  $\geq 7.0$  mmol/l for patients who had fasted 4 hours or  $\geq 11.1$  mmol/l for nonfasting patients. Serum LDL was calculated using the Friedewald formula.<sup>22</sup> High LDL was defined as serum level of  $\geq 2.5$  mmol/l.<sup>23</sup> Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters. Obesity was defined as a BMI  $\geq 30.0$  kg/m<sup>2</sup>, according to World Health Organization guidelines.<sup>24</sup> Medication was coded according to the Anatomical Therapeutic Chemical (ATC) Classification System.

### Kidney Function Assessment

At baseline and 41-month follow-up, serum cystatin C (cysC) was measured from stored blood samples in a central laboratory. We used calibrators and assays of the same lot code, which was stable (no downward drift).<sup>25</sup> Serum creatinine (cr) was measured by the modified kinetic Jaffé method, as previously described in detail.<sup>25</sup> We estimated glomerular filtration rate based on cystatin C (eGFR<sub>cysC</sub>) and combined creatinine–cystatin C (eGFR<sub>cr-cysC</sub>) at baseline and after 41 months, using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations from 2012, taking into account age, sex, and race.<sup>26</sup> Both eGFR<sub>cysC</sub> and eGFR<sub>cr-cysC</sub> are regarded as superior measures of kidney function

compared to eGFR based on creatinine alone. In the main analyses, we use eGFR<sub>cysC</sub> as outcome; results for eGFR<sub>cr-cysC</sub> as outcome are reported in [Supplementary Tables S1 to S3](#). From each individual, eGFR decline was calculated by subtracting the eGFR at baseline from the eGFR after 41 months. Assuming a linear decline over time, we then estimated the annual kidney function decline. Rapid kidney function decline was defined as an annual decline of  $>3$  ml/min per  $1.73 \text{ m}^2$ .<sup>27,28</sup>

### Data Analysis

Baseline characteristics are presented for all patients and according to the number of cardiovascular risk factors. Baseline data are presented as mean (SD), median (interquartile range), or number (percentage) when appropriate. The following data were missing: LDL cholesterol ( $n = 116$ ), BMI ( $n = 4$ ), level of education ( $n = 4$ ), blood pressure ( $n = 3$ ), and alcohol consumption ( $n = 3$ ). We accounted for missing data by multiple imputation, using 5 imputations, and including all relevant baseline variables and the outcome in the model.

We used analysis of covariance to compare annual eGFR<sub>cysC</sub> decline rates for presence versus absence of *a priori*–selected cardiovascular risk factors (including unhealthy lifestyle): diabetes, high blood pressure, high LDL levels, current cigarette smoking, and obesity. In addition, we used multivariable logistic regression to estimate for each cardiovascular risk factor the risk of rapid kidney function decline. In all analyses, we used patients without the cardiovascular risk factor as the reference. All analyses are presented crude and adjusted for potential confounders: age, sex, and 3 dummy variables for the four *n*-3–fatty acid treatment groups of the Alpha Omega Trial (model 1). In model 2 we adjusted in addition to model 1, for alcohol use ( $<1$  vs.  $\geq 1$  glass per week), level of education (3 dummy variables), and the 5 *a priori*–selected cardiovascular risk factors. Analyses for obesity were not adjusted for diabetes, high blood pressure, and high LDL, because these factors are in the causal pathway between obesity and kidney function decline. Analyses were not adjusted for baseline eGFR, because baseline adjustment in models with change scores as dependent variable results in biased and inflated estimates.<sup>29</sup> We explored the presence of effect modification between age or sex and the modifiable risk factors with regard to kidney function decline by including interaction terms in our linear regression models. Furthermore, we repeated analyses in strata of baseline eGFR (eGFR  $<60$ ,  $60$  to  $<90$ ,  $\geq 90$  ml/min per  $1.73 \text{ m}^2$ ).

Finally, we calculated the rate of kidney function decline and risk of rapid kidney function decline according to the number of cardiovascular risk factors present in each patient. In these analyses, we included

diabetes, high blood pressure, current smoking, and obesity. High LDL was excluded because of lack of evidence that modifying LDL level affects cardiovascular risk.<sup>30</sup> Patients without cardiovascular risk factors have, by definition, an optimal cardiovascular risk profile and a healthy lifestyle (e.g., are considered being optimally treated for the included risk factors according to the latest guidelines of the European Society of Cardiology: blood pressure  $<140/90$  mm Hg, no diabetes, never smoked cigarettes or ceased smoking, and no obesity (BMI  $<30 \text{ kg/m}^2$ ).<sup>31</sup> A linear trend was evaluated by including a variable representing number of cardiovascular risk factors into the linear regression model.

### Sensitivity Analyses

We repeated all analyses without multiple imputation, using a complete case analysis. Next, we repeated the analyses adjusting for continuous instead of dichotomized variables, for example, for BMI instead of obesity, and for systolic blood pressure instead of high blood pressure. Main analyses were repeated after adjustment for time since MI, hsCRP levels, or use of renin–angiotensin system (RAS)–blocking drugs. We repeated the analyses in patients persistently (at baseline and after 41 months of follow-up) using RAS-blocking drugs. Finally, we repeated the main analyses using eGFR<sub>cr-cysC</sub> as outcome. In these analyses, we excluded 82 patients for whom serum creatinine was not available because of technical failure or analytical disturbance.<sup>25</sup> We considered 2-sided *P* values  $<0.05$  statistically significant. All analyses were performed using SPSS 23.0 (SPSS, Inc., Chicago, IL).

## RESULTS

### Baseline Characteristics

Baseline characteristics of all patients ( $n = 2426$ ), and stratified for the number of cardiovascular and lifestyle risk factors, are presented in [Table 1](#). The mean (SD) age of the total study cohort was 68.9 (5.4) years, 79.4% were men, median time since MI was 4.0 years, and mean (SD) eGFR<sub>cysC</sub> and eGFR<sub>cr-cysC</sub> were 81.5 (19.6) and 78.5 (18.7) ml/min per  $1.73 \text{ m}^2$ , respectively. Of all patients, 23% were obese, 16% were current smokers, 67% were former smokers, 44% had a blood pressure within the target range, 87% used antihypertensive medication, 54% used RAS-blocking drugs (of whom 92% persisted on RAS-blocking drugs), and 19% had diabetes (of whom 71% used glucose-lowering medication). Finally, 44% of patients had normal LDL and 85% used statins (of whom 95% persisted on statins). Of all patients with high LDL ( $n = 990$ ) at baseline, 10% started with a statin during follow-up.



**Table 1.** Baseline characteristics of 2426 post-MI patients of the Alpha Omega Cohort according to the number of cardiovascular risk factors (obesity, high blood pressure, diabetes, current smoking)

Baseline variable	All patients n = 2426	Number of cardiovascular risk factors			
		0 n = 598	1 n = 1088	2 n = 573	≥3 n = 167
Age, yr	68.9 ± 5.4	68.3 ± 5.3	69.6 ± 5.4	68.5 ± 5.5	68.9 ± 5.4
Men, n (%)	1927 (79.4)	497 (83.1)	878 (80.7)	430 (75.0)	122 (73.1)
Race, white, n (%)	2398 (98.8)	589 (98.5)	1078 (99.1)	567 (99.0)	164 (98.2)
Time since MI, yr	4.0 (2.0–6.4)	3.3 (1.6–5.9)	4.0 (1.9–6.5)	4.4 (2.4–6.6)	4.8 (3.1–7.4)
Educational level, n (%)					
Only elementary/low	1374 (57.0)	319 (53.6)	603 (55.7)	353 (62.0)	99 (59.6)
Moderate	738 (30.6)	190 (31.9)	344 (31.8)	152 (26.7)	52 (31.3)
High <sup>a</sup>	300 (12.4)	86 (14.5)	135 (12.5)	64 (11.2)	15 (9.0)
Current smoking, n (%)	386 (15.9)	0	100 (9.2)	196 (34.2)	90 (53.9)
Alcohol consumption, <sup>b</sup> n (%)	1759 (72.5)	450 (75.3)	813 (74.7)	390 (68.1)	106 (63.5)
Obesity, <sup>c</sup> n (%)	554 (22.8)	0	146 (13.4)	268 (46.8)	140 (83.8)
Body mass index, kg/m <sup>2</sup>	27.7 ± 3.6	26.0 ± 2.3	27.1 ± 3.1	29.3 ± 4.1	32.1 ± 3.5
High blood pressure, <sup>d</sup> n (%)	1064 (43.9)	0	744 (68.4)	457 (79.8)	161 (96.4)
Systolic blood pressure, mm Hg	143.3 ± 21.4	125.1 ± 10.3	147.6 ± 21.6	150.8 ± 19.6	154.8 ± 17.7
Diastolic blood pressure, mm Hg	81.4 ± 10.8	75.1 ± 7.8	83.1 ± 10.9	83.2 ± 10.8	86.3 ± 9.4
Antihypertensive drugs, <sup>e</sup> n (%)	2111 (87.0)	502 (83.9)	954 (87.7)	507 (88.5)	148 (88.6)
ACE inhibitors/ATII blockers	1309 (54.0)	311 (52.0)	576 (52.9)	327 (57.1)	95 (56.9)
β-Blockers	1585 (65.3)	371 (62.0)	718 (66.0)	385 (67.2)	111 (66.5)
Calcium channel blockers	467 (19.2)	111 (18.6)	200 (18.4)	117 (20.4)	39 (23.4)
Diuretics	500 (20.6)	99 (16.6)	198 (18.2)	162 (28.3)	41 (24.6)
Diabetes, <sup>f</sup> n (%)	449 (18.5)	0	98 (9.0)	225 (39.3)	126 (75.4)
Plasma glucose, <sup>g</sup> mmol/l	6.0 ± 2.0	5.4 ± 1.0	5.7 ± 1.4	6.7 ± 2.4	8.2 ± 3.2
Glucose-lowering drugs, <sup>h</sup> n (%)	320 (13.2)	0	72 (6.6)	169 (29.5)	79 (47.3)
Oral glucose-lowering drugs	253 (10.4)	0	56 (5.1)	135 (23.6)	62 (37.1)
Insulin analogues	107 (4.4)	0	25 (2.3)	52 (9.1)	30 (18.0)
Serum LDL, <sup>i</sup> mmol/l	2.74 ± 0.80	2.68 ± 0.81	2.74 ± 0.79	2.75 ± 0.79	2.86 ± 0.87
Lipid-modifying drugs, <sup>j</sup> n (%)	2089 (86.1)	518 (86.6)	938 (86.2)	485 (84.6)	148 (88.6)
Statins	2073 (85.4)	516 (86.3)	933 (85.8)	478 (83.4)	146 (87.4)
Antithrombotic agents, <sup>k</sup> n (%)	2368 (97.6)	583 (97.5)	1060 (97.4)	560 (97.7)	165 (98.8)
Serum hsCRP, mg/l	1.7 (0.8–3.6)	1.2 (0.6–2.8)	1.5 (0.8–3.3)	2.3 (1.1–4.6)	2.9 (1.2–5.2)
Serum cystatin C, mg/l	0.97 ± 0.24	0.93 ± 0.20	0.97 ± 0.24	1.01 ± 0.28	0.97 ± 0.24
Serum creatinine, <sup>l</sup> μmol/l	90.1 ± 29.3	89.2 ± 25.0	90.0 ± 30.4	92.7 ± 32.1	82.1 ± 26.1
eGFR <sub>cysC</sub> , <sup>m</sup> ml/min per 1.73 m <sup>2</sup>	81.5 ± 19.5	84.9 ± 17.9	81.0 ± 19.3	78.7 ± 20.8	81.7 ± 20.5
eGFR <sub>cr-cysC</sub> , <sup>m</sup> ml/min per 1.73 m <sup>2</sup>	78.5 ± 18.7	80.8 ± 17.1	78.4 ± 18.6	75.8 ± 19.8	80.1 ± 19.7

ACE, angiotensin-converting enzyme; ATII, angiotensin II; eGFR<sub>cr-cysC</sub>, glomerular filtration rate estimated by combined creatinine–cystatin C; eGFR<sub>cysC</sub>, glomerular filtration rate estimated by serum cystatin C; hsCRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein; MI, myocardial infarction.

<sup>a</sup>Higher vocational education or university.

<sup>b</sup>At least 1 glass per week.

<sup>c</sup>Body mass index ≥30 kg/m<sup>2</sup>.

<sup>d</sup>Systolic blood pressure of ≥140 mm Hg and/or diastolic blood pressure of ≥90 mm Hg, irrespective of use of blood pressure–lowering drugs.

<sup>e</sup>Blood pressure–lowering drugs: Anatomical Therapeutic Chemical Classification System (ATC) codes C02, C03, C07, C08, and C09.

<sup>f</sup>Self-reported diagnosis by a physician, use of glucose-lowering drugs, or hyperglycemia.

<sup>g</sup>To convert the values for glucose to milligrams per deciliter (mg/dl), divide by 0.05551.

<sup>h</sup>Glucose-lowering drugs: ATC codes A10, A10A, A10B, A10X.

<sup>i</sup>To convert the values for LDL-cholesterol to milligrams per deciliter (mg/dl), divide by 0.02586.

<sup>j</sup>Lipid-modifying drugs: ATC codes C10 and C10AA.

<sup>k</sup>Antithrombotic agents: ATC code B01.

<sup>l</sup>To convert the values for creatinine to milligrams per deciliter (mg/dl), divide by 88.40.

<sup>m</sup>eGFR<sub>cysC</sub> and eGFR<sub>cr-cysC</sub> based on the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations from 2012.

Data are reported as number of patients (%), mean ± SD, or median (interquartile range).

## Kidney Function Decline

After 41 months of follow-up, the mean (95% confidence interval [CI]) eGFR<sub>cysC</sub> decline for all patients was  $-4.62$  ( $-5.06$  to  $-4.18$ ) ml/min per 1.73 m<sup>2</sup>, corresponding to an annual decline of  $-1.34$  ( $-1.47$  to  $-1.21$ ) ml/min per 1.73 m<sup>2</sup>. Men and women had annual kidney function decline rates of  $-1.45$  ( $-1.59$  to  $-1.31$ ) and  $-0.91$  ( $-1.19$  to  $-0.63$ ) ml/min per 1.73 m<sup>2</sup>, respectively. Patients

younger than 70 years versus those 70 years or older had annual kidney function decline rates of  $-1.15$  ( $-1.32$  to  $-0.98$ ) and  $-1.60$  ( $-1.80$  to  $-1.41$ ) ml/min per 1.73 m<sup>2</sup>, respectively. After multivariable adjustment (model 2), patients without or with diabetes had an annual eGFR<sub>cysC</sub> decline of  $-1.17$  ( $-1.31$  to  $-1.03$ ) and  $-2.07$  ( $-2.37$  to  $-1.78$ ) ml/min per 1.73 m<sup>2</sup> (difference,  $-0.90$  ( $-1.23$  to  $-0.57$ )) (Table 2). Patients with normal or high

**Table 2.** Mean (95% CI) annual cystatin C–based eGFR decline rates in 2426 post–myocardial infarction patients according to absence or presence of cardiovascular risk factors

Risk factor	n	Crude	Model 1	Model 2
Diabetes				
No (reference)	1977	–1.17 (–1.31 to –1.03)	–1.17 (–1.31 to –1.03)	–1.17 (–1.31 to –1.03)
Yes	449	–2.06 (–2.36 to –1.77) <sup>b</sup>	–2.10 (–2.40 to –1.81) <sup>b</sup>	–2.07 (–2.37 to –1.78) <sup>b</sup>
Blood pressure				
<140/90 mm Hg (reference)	1062	–1.01 (–1.20 to –0.82)	–1.01 (–1.20 to –0.82)	–1.01 (–1.20 to –0.82)
≥140/90 mm Hg	1364	–1.59 (–1.76 to –1.42) <sup>b</sup>	–1.51 (–1.69 to –1.34) <sup>b</sup>	–1.51 (–1.69 to –1.34) <sup>b</sup>
Serum LDL				
<2.5 mmol/l (reference)	990	–1.47 (–1.67 to –1.27)	–1.47 (–1.67 to –1.27)	–1.47 (–1.67 to –1.27)
≥2.5 mmol/l	1436	–1.25 (–1.41 to –1.08)	–1.29 (–1.46 to –1.12)	–1.28 (–1.45 to –1.12)
Cigarette smoking				
Nonsmoking (reference)	2040	–1.32 (–1.46 to –1.18)	–1.32 (–1.46 to –1.18)	–1.32 (–1.46 to –1.18)
Currently smoking	386	–1.43 (–1.75 to –1.11)	–1.54 (–1.86 to –1.22)	–1.51 (–1.83 to –1.18)
Body mass index				
<30.0 kg/m <sup>2</sup> (reference)	1871	–1.30 (–1.45 to –1.16)	–1.30 (–1.45 to –1.16)	–1.30 (–1.45 to –1.16)
≥30.0 kg/m <sup>2</sup>	555	–1.46 (–1.72 to –1.19)	–1.62 (–1.89 to –1.35) <sup>a</sup>	–1.61 (–1.88 to –1.34)

CI, confidence interval; eGFR, estimated glomerular filtration rate; LDL, low-density lipoprotein.

<sup>a</sup> $P < 0.05$ .<sup>b</sup> $P < 0.001$  for difference between presence versus absence of risk factor.

Adjusted variables were fixed at the mean value of the reference group; hence the estimates of the reference category are equal across models. Diabetes was defined as self-reported diagnosis by a physician, use of glucose-lowering drugs, or elevated plasma glucose level. Model 1: adjusted for age, sex, and treatment group. Model 2: model 1 plus additional adjustment for current smoking, alcohol consumption, level of education, diabetes, high blood pressure, high LDL, and obesity. Analyses for obesity were not adjusted for diabetes, high blood pressure, and high LDL.

blood pressure had annual decline rates of  $-1.01$  ( $-1.20$  to  $-0.82$ ) and  $-1.51$  ( $-1.69$  to  $-1.34$ ) ml/min per  $1.73 \text{ m}^2$  (difference,  $-0.50$  ( $-0.76$  to  $-0.24$ )). Successive quartiles of systolic blood pressure (quartile ranges: 86.5–128.0, 128.5–141.5, 142.0–156.5, and 157.0–237.5 mm Hg) showed a faster annual kidney function decline:  $-0.99$  ( $-1.25$  to  $-0.74$ ),  $-1.10$  ( $-1.34$  to  $-0.85$ ),  $-1.45$  ( $-1.70$  to  $-1.20$ ), and  $-1.82$  ( $-2.07$  to  $-1.57$ ) ml/min per  $1.73 \text{ m}^2$ , respectively. Each systolic blood pressure increment of 10 mm Hg was associated with an extra annual kidney function decline of  $-0.17$  ( $-0.23$  to  $-0.12$ ,  $P < 0.001$ ) ml/min per  $1.73 \text{ m}^2$ . We found a weak U-shaped relation between diastolic blood pressure and kidney function decline. Annual kidney function decline for patients in the lowest through the highest quartile was  $-1.33$  ( $-1.59$  to  $-1.08$ ),  $-1.15$  ( $-1.40$  to  $-0.91$ ),  $-1.32$  ( $-1.58$  to  $-1.06$ ), and  $-1.55$  ( $-1.80$  to  $-1.30$ ) ml/min per  $1.73 \text{ m}^2$  (quartile ranges: 44.0–73.5, 74.0–81.0, 81.5–88.0, and 88.5–124.0 mm Hg). We found no significant difference in the rate of annual kidney function decline between patients with high compared to normal LDL levels. Cigarette smokers compared to nonsmokers had an additional annual eGFR<sub>cysC</sub> decline of  $-0.19$  ( $-0.54$  to  $0.16$ ) ml/min per  $1.73 \text{ m}^2$ . Obesity was associated with a 23% faster kidney function decline (Table 2). We found no evidence for effect modification between sex, age, strata of baseline kidney function, and the prespecified cardiovascular risk factors with regard to eGFR<sub>cysC</sub> decline.

Of all patients, 573 (24.4%) had a rapid kidney function decline. Table 3 shows the odds ratios (ORs) for rapid kidney function decline according to the *a*

*priori* –selected cardiovascular risk factors. Especially, diabetes (OR 1.72 [1.36–2.17]) and high blood pressure (OR 1.43 [1.18–1.74]) were strongly associated with rapid kidney function decline. Associations for current smoking (OR 1.21 [0.94–1.57]) and obesity (OR 1.15 [0.92–1.45]) were weaker. High LDL was associated with slower kidney function decline (OR 0.80 [0.66–0.98]). Results were comparable when defining rapid kidney function decline as  $>5$  ml/min per  $1.73 \text{ m}^2$  per year (data not shown). Furthermore, after adjustment for age and treatment group, men had a slightly higher risk of rapid kidney function decline than women (OR 1.13 [0.89–1.43]). After adjustment for sex and treatment

**Table 3.** Odds ratios (95% CI) for risk of rapid eGFR<sub>cysC</sub> decline ( $>3$  ml/min per  $1.73 \text{ m}^2$  per year) in 2426 post–myocardial infarction patients, for different cardiovascular risk factors

Risk factor <sup>a</sup>	Crude	Model 1	Model 2
Diabetes	1.77 (1.41–2.21) <sup>b</sup>	1.79 (1.43–2.25) <sup>b</sup>	1.72 (1.36–2.17) <sup>b</sup>
High blood pressure	1.48 (1.22–1.79) <sup>b</sup>	1.41 (1.17–1.72) <sup>b</sup>	1.43 (1.18–1.74) <sup>b</sup>
High LDL	0.81 (0.67–0.98) <sup>c</sup>	0.82 (0.68–0.99) <sup>c</sup>	0.80 (0.66–0.98) <sup>c</sup>
Current cigarette smoking	1.13 (0.88–1.45)	1.23 (0.95–1.58)	1.21 (0.94–1.57)
Obesity	1.09 (0.88–1.36)	1.17 (0.93–1.46)	1.15 (0.92–1.45)

CI, confidence interval; eGFR<sub>cysC</sub>, glomerular filtration rate estimated by serum cystatin C; LDL, low-density lipoprotein.Diabetes was defined as self-reported diagnosis by a physician, use of glucose-lowering drugs, or hyperglycemia. High blood pressure was defined as systolic blood pressure of  $\geq 140$  mm Hg and/or diastolic blood pressure of  $\geq 90$  mm Hg, irrespective of use of blood pressure lowering drugs. High LDL was defined as serum LDL level of  $\geq 2.5$  mmol/l. Obesity was defined as BMI of  $\geq 30.0 \text{ kg/m}^2$ . Model 1: adjusted for age, sex, and treatment group. Model 2: model 1 plus additional adjustment for current smoking, alcohol consumption, level of education, diabetes, high blood pressure, high LDL, and obesity. Analyses for obesity were not adjusted for diabetes, high blood pressure, and high LDL.<sup>a</sup>Reference: absence of the risk factor of interest.<sup>b</sup> $P < 0.001$ .<sup>c</sup> $P < 0.05$ .

group, older compared to younger patients had more often rapid kidney function decline (age  $\geq 70$  years vs.  $< 70$  years, OR 1.32 [1.09–1.59]; age  $\geq 75$  years vs.  $< 75$  years, OR 1.59 [1.25–2.02]).

### Kidney Function Decline and Number of Risk Factors

We calculated the annual kidney function decline and risk for rapid kidney function decline in each patient according to the number of cardiovascular risk factors, namely, diabetes, high blood pressure, current cigarette smoking, and obesity (BMI  $\geq 30$  kg/m<sup>2</sup>). Patients without any of these cardiovascular risk factors present (thus considered to have optimal cardiovascular parameters and a healthy lifestyle) had an annual kidney function decline of  $-0.90$  ( $-1.16$  to  $-0.65$ ) ml/min per 1.73 m<sup>2</sup> (Table 4, Figure 1). Each additional cardiovascular risk factor was associated with a progressively faster annual kidney function decline (linear regression coefficient  $-0.45$  [ $-0.59$  to  $-0.30$ ] per additional risk factor,  $P$  for linear trend  $< 0.001$ ). Patients in whom 3 or more cardiovascular risk factors were present had an annual kidney function decline of  $-2.37$  ( $-2.85$  to  $-1.89$ ) ml/min per 1.73 m<sup>2</sup>. Patients in whom all 4 cardiovascular risk factors ( $n = 16$ ) were present had an annual kidney function decline of  $-4.59$  ( $-5.38$  to  $-3.79$ ) ml/min per 1.73 m<sup>2</sup>. Risk for rapid kidney function decline increased progressively with every additional cardiovascular risk factor (Table 4, Figure 1). Patients with  $\geq 3$  cardiovascular risk factors had a 2.5-fold increased risk compared to patients without any cardiovascular risk factors.

### Sensitivity Analyses

Results did not materially change when using complete cases only instead of multiple imputed data. Adjustment with continuous instead of dichotomized variables did not change the results. Adjustment for time

since MI, serum hsCRP, or use of RAS-blocking drugs yielded similar results. Confining analyses to patients who persistently used RAS-blocking drugs ( $n = 1206$ ) yielded comparable associations. Analyses based on eGFR<sub>cr-cysC</sub> as outcome showed slightly weaker effect estimates (Supplementary Tables S1 and S2). The association between the number of cardiovascular risk factors and annual eGFR<sub>cr-cysC</sub> or eGFR<sub>cysC</sub> decline was comparable (Supplementary Table S3).

## DISCUSSION

In a cohort of stable, older post-MI patients, we showed that those patients with optimally treated cardiovascular risk factors, including healthy lifestyle, had an annual kidney function decline of about  $-0.90$  ml/min per 1.73 m<sup>2</sup>. In contrast, post-MI patients with 3 or more suboptimally treated cardiovascular risk factors had a 2.5-fold faster annual kidney function decline of about  $-2.37$  ml/min per 1.73 m<sup>2</sup>. We recently showed that in these post-MI patients, an eGFR<sub>cysC</sub> of  $< 80$  ml/min per 1.73 m<sup>2</sup> is a graded risk factor for cardiovascular and all-cause mortality, underlining the clinical relevance of these findings.<sup>2,28</sup>

The mean annual kidney function decline of  $-0.90$  ( $-1.16$  to  $-0.65$ ) ml/min per 1.73 m<sup>2</sup> that we found in optimally treated cardiac patients with a healthy lifestyle is within the normal range of the age-related kidney function decline in healthy individuals of  $-1.0$  ml/min per 1.73 m<sup>2</sup>.<sup>32–34</sup> The mean (95% CI) annual kidney function decline of all patients was  $-1.34$  ( $-1.47$  to  $-1.21$ ) ml/min per 1.73 m<sup>2</sup>. Previously, the Prevention of Renal and Vascular Endstage Disease (PREVEND) study showed, in post-MI patients, an annual kidney function decline (95% CI) of  $-2.2$  ( $-5.0$  to  $-0.9$ ) ml/min per 1.73 m<sup>2</sup>.<sup>5</sup> Post-MI patients in the PREVEND study had a cardiovascular risk profile similar to that of patients in the Alpha Omega Cohort.

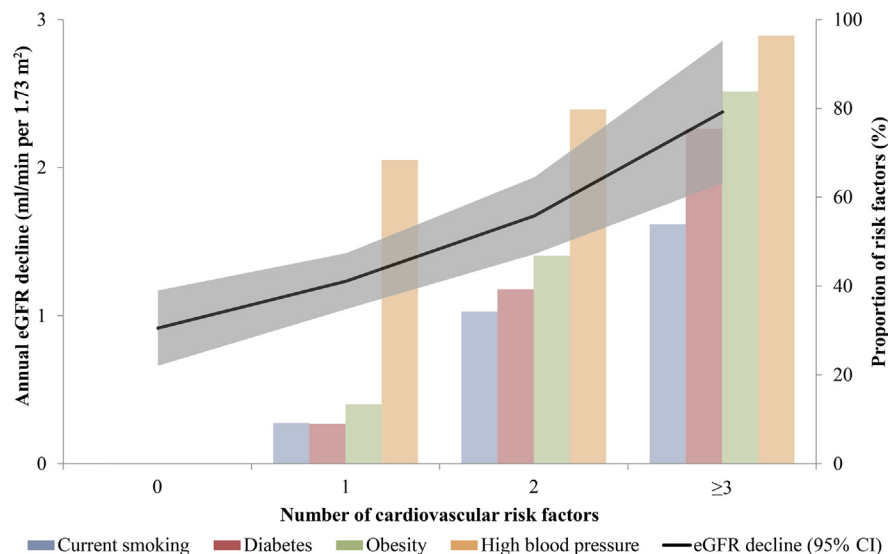
**Table 4.** Mean (95% CI) annual eGFR<sub>cysC</sub> decline and odds ratios (95% CIs) for rapid eGFR<sub>cysC</sub> decline ( $> 3$  ml/min per 1.73 m<sup>2</sup> per year) are presented per number of cardiovascular risk factors<sup>a</sup>, in 2426 post-myocardial infarction patients of the Alpha Omega Cohort

Number of risk factors <sup>a</sup>	n		Crude	Model 1	Model 2
0 (reference)	597	Annual eGFR <sub>cysC</sub> decline	$-0.90$ ( $-1.16$ to $-0.65$ )	$-0.90$ ( $-1.16$ to $-0.65$ )	$-0.90$ ( $-1.16$ to $-0.65$ )
1	1088		$-1.29$ ( $-1.48$ to $-1.10$ )	$-1.23$ ( $-1.42$ to $-1.03$ )	$-1.23$ ( $-1.42$ to $-1.03$ )
2	574		$-1.61$ ( $-1.87$ to $-1.35$ )	$-1.66$ ( $-1.92$ to $-1.40$ )	$-1.65$ ( $-1.91$ to $-1.39$ )
$\geq 3$	167		$-2.26$ ( $-2.74$ to $-1.77$ )	$-2.37$ ( $-2.85$ to $-1.88$ )	$-2.37$ ( $-2.85$ to $-1.89$ )
0 (reference)	597	Odds ratio rapid eGFR <sub>cysC</sub> decline	1	1	1
1	1088		1.14 (0.89–1.46)	1.09 (0.85–1.40)	1.09 (0.85–1.40)
2	574		1.55 (1.18–2.03)	1.57 (1.19–2.06)	1.56 (1.19–2.06)
$\geq 3$	167		2.41 (1.66–3.49)	2.55 (1.77–3.71)	2.55 (1.75–3.71)

CI, confidence interval; eGFR<sub>cysC</sub>, glomerular filtration rate estimated by serum cystatin C.

<sup>a</sup>Cardiovascular risk factors included diabetes, high blood pressure, obesity, and current smoking.

Adjusted variables were fixed at the mean value of the reference group; hence the estimates of the reference category are equal across models. Diabetes was defined as self-reported diagnosis by a physician, use of glucose-lowering drugs, or hyperglycemia. High blood pressure was defined as systolic blood pressure of  $\geq 140$  mm Hg and/or diastolic blood pressure of  $\geq 90$  mm Hg, irrespective of use of blood pressure-lowering drugs. Obesity was defined as BMI of  $\geq 30.0$  kg/m<sup>2</sup>. Model 1: adjusted for age, sex, and treatment group. Model 2: model 1 plus additional adjustment for alcohol consumption and level of education.



**Figure 1.** Annual  $eGFR_{cysC}$  decline according to the number of cardiovascular risk factors, in 2426 post-myocardial infarction patients in the Alpha Omega Cohort. For the 4 groups according to the number of cardiovascular risk factors (diabetes, high blood pressure, obesity, and current smoking), the proportion (%) of the 4 different risk factors (columns, right vertical axis) and the mean (95% confidence interval [CI]) annual  $eGFR_{cysC}$  decline (black line, left vertical axis), adjusted for age, sex, and treatment group, are presented.  $eGFR$ , estimated glomerular filtration rate;  $eGFR_{cysC}$ , glomerular filtration rate estimated by serum cystatin C.

There are several explanations that may have resulted in the higher annual kidney function decline in the PREVEND compared to the Alpha Omega Cohort. First, the small number ( $n = 66$ ) of post-MI patients in the PREVEND study resulted in a wide 95% confidence interval, and, as a consequence, the effect estimate is less precise. Patients from the Alpha Omega Cohort participated in a trial for 41 months. Trial patients generally are healthier and more compliant compared to the general population, a phenomenon known as volunteer bias.<sup>35</sup> Finally, during follow-up, patients in the Alpha Omega Cohort (2002–2009) have been more strictly controlled according to more recent secondary prevention guidelines, compared to patients in the PREVEND cohort (1997–2005). In updated guidelines, there was more attention given especially to patient education, lifestyle monitoring (e.g., smoking cessation, weight management), diabetes and high blood pressure management, more strict lipid regulation, and standard prescription of statins and angiotensin-converting enzyme inhibitors.<sup>36,37</sup>

In agreement with other studies, we found that diabetes and high blood pressure were strongly associated with accelerated kidney pressure function decline.<sup>7–10</sup> Diabetes may lead to diabetic nephropathy, a complex disease characterized by hemodynamic, metabolic, and inflammatory changes, ultimately leading to progressive interstitial fibrosis and glomerular damage.<sup>38</sup> High blood pressure may cause increased intraglomerular pressure, leading to endothelial dysfunction, loss of adequate autoregulation, and eventually to progressive glomerular and interstitial fibrosis.<sup>39</sup> We found a weak

association between high LDL level and slower kidney function decline, but this association may be distorted by the fact that 85% of all patients used statins. Moreover, of all patients with high LDL at baseline, 10% started with a statin during follow-up. Our finding is in accordance with recent guidelines stating that CKD patients  $\geq 50$  years of age should be treated with a statin independent of lipid levels, without trying to reach a target level.<sup>40</sup> This paradigm shift is caused by the lack of evidence linking changes in lipid levels with actual cardiovascular risk and emerging evidence showing pleiotropic effects of statins.<sup>30,41,42</sup>

In line with other studies, we found that obesity was associated with faster kidney function decline.<sup>8,43</sup> Obesity promotes deterioration of kidney function through cardiovascular risk factors such as diabetes and hypertension, and is also associated with visceral fat accumulation and accompanying inflammation, leading to glomerular and interstitial fibrosis.<sup>12,13,24</sup> Furthermore, we found that smoking of cigarettes was associated with kidney function decline, which is confirmed by other studies.<sup>44</sup> However, the association of smoking and kidney function decline was weaker than expected, and could be underestimated due to underreporting, or so-called information bias.

Our study has some limitations. First, the observational design prevents us from making causal inferences. Second, kidney function was estimated at only 2 time points and was not directly measured. Third, we had no information about proteinuria, an important independent predictor of kidney function; therefore, we could not study the association between optimal treatment of



cardiovascular risk factors and change in proteinuria. Fourth, about 17% of patients dropped out because of missing samples, refusal of participation, or death. If anything, this may have resulted in underestimation of the associations that we found, as patients who dropped out were most likely less healthy. Fifth, volunteer bias may be present, as we included only trial patients. However, because volunteering patients usually are more healthy, we expect that this may have led to an underestimation of our results. Finally, we analyzed post-MI patients only, which may hamper the generalizability of our results. Notably, the prevalence of cardiovascular disease shows an increasing trend worldwide, and our cohort of patients therefore represents a growing patient group.

A major strength of this study is our large homogeneous population of post-MI patients, which provides a unique opportunity to study the course of kidney function decline in these patients. Second, we used as outcomes both eGFR<sub>cysC</sub> and eGFR<sub>cr-cysC</sub>, which are currently the most accurate methods available to estimate kidney function.<sup>26,28,45</sup>

To conclude, we found a faster rate of kidney function decline in post-MI patients with an increasing number of insufficiently treated cardiovascular risk factors (including unhealthy lifestyle). Post-MI patients with optimal cardiovascular and lifestyle parameters have an annual kidney function decline comparable to that of the general population. Further research is needed to investigate whether optimization of cardiovascular risk factors and healthy lifestyle may slow down the accelerated kidney function decline in post-MI patients.

## DISCLOSURE

EKH is a member of the Guideline Committee of the Dutch Federation of Nephrology. JMG received research funding from Unilever R&D for epidemiological studies of dietary fatty acids and is a member of the Standing Committee on Nutrition of the Dutch Health Council, Working Group on Minerals of the European Food and Safety Authority, and Dutch Academy for Nutritional Sciences, and is a Fellow of the American Heart Association. DK received research funding from the Royal Netherlands Academy of Arts and Sciences and is Member of the Dutch Academy of Nutritional Sciences. All the other authors declared no competing interests.

## ACKNOWLEDGMENTS

The Alpha Omega Cohort Study is registered at [ClinicalTrials.gov](https://clinicaltrials.gov) (no. NCT03192410) <https://clinicaltrials.gov/ct2/show/NCT03192410>, <http://alphaomegatrial.com/methods>. Results from this study have been previously presented at the ERA-EDTA Congress in Madrid, June 2017

(poster 55-SP) and at the Dutch Nephrology Days (NND) March 2017.

Financial support was obtained from the Dutch Kidney Foundation (PV41; EKH), the Dutch Heart Foundation (JMG and DK) and the National Institutes of Health (JMG and DK). The grant from the Dutch Kidney Foundation covered baseline and final examinations of kidney function. The grant from the Dutch Heart Foundation covered baseline examinations. The grant from the National Institutes of Health covered final examinations.

## AUTHOR CONTRIBUTIONS

KE, JMG, DK, and EKH contributed to conception and design of the manuscript. KE, JMG, EKH, DK, and EKH contributed to acquisition, analysis and interpretation, and drafted the manuscript. JWdF contributed to interpretation. All authors critically revised the manuscript, all gave final approval and all agreed to be accountable for all aspects of work, ensuring integrity and accuracy.

## SUPPLEMENTARY MATERIAL

**Figure S1.** Flow chart of 2426 post-MI patients included in the present study.

**Table S1.** Mean (95% CI) annual creatinine–cystatin C–based eGFR decline rates in 2344 post-MI patients according to absence or presence of cardiovascular risk factors.

**Table S2.** Odds ratios (95% CI) for risk of rapid creatinine–cystatin C–based eGFR decline (>3 ml/min per 1.73 m<sup>2</sup> per year) in 2344 post-MI patients, for different cardiovascular risk factors.

**Table S3.** Mean (95% CI) annual creatinine–cystatin C–based eGFR decline and odds ratios (95% CI) for rapid creatinine–cystatin C–based eGFR decline (>3 ml/min per 1.73 m<sup>2</sup> per year) per number of cardiovascular risk factors, in 2344 post-MI patients in the Alpha Omega Cohort. Supplementary material is linked to the online version of the paper at [www.kireports.org](http://www.kireports.org).

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